

Preliminary Research

Sustained-Release Oxycodone Tablets for Moderate to Severe Painful Diabetic Peripheral Neuropathy: A Multicenter, Open-Labelled, Postmarketing Clinical Observation

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Abstract

Objective. To evaluate the efficacy and safety of sustained-release (SR) oxycodone tablets in the treatment of moderate to severe painful diabetic peripheral neuropathy (DPN).

Design. This was a multicenter, randomized, open-labeled study.

Setting. This study was completed in 12 hospitals in China.

Patients. A total of 80 Chinese patients undergoing moderate to severe painful DPN.

Interventions. An initial dose of 10 mg is recommended to be taken orally every 12 hours. Dose titration was done appropriately according to pain intensity and adverse reactions.

Outcome Measures. Data record included days, dosage, analgesic efficacy, quality of sleep, adverse events, and combination therapy when patients were treated with SR oxycodone tablets. The continuous observation period was 6 weeks.

Results. After medication for 1 week, pain was significantly ($P < 0.01$) relieved from 6.8 ± 1.4 to 2.8 ± 1.6 . Onset time was within 45 minutes in nearly 60% of the patients, and within 1 hour in nearly 95% of that ones. More than 90% of the patients achieved stable analgesic dose within 3 days. After using SR oxycodone tablets for 1 week, sleep quality was significantly ($P < 0.01$) improved. In week 1, the average dose of SR oxycodone tablets was 16.63 ± 7.79 mg. The average daily dose of most

patients was about 20 mg after 2 weeks. In all the enrolled patients, 38 (47.5%) had adverse reactions. No serious adverse reactions took place.

Conclusion. The results of this clinical observation further elaborated the efficacy and safety of SR oxycodone tablets in the treatment of moderate to severe painful diabetic peripheral neuropathy in China.

Key Words. Diabetic Peripheral Neuropathy; Pain; Analgesic; Sustained-Release Oxycodone; Opioid; Adverse Reactions

Introduction

Diabetic peripheral neuropathy (DPN) occurs in up to 50% of patients with diabetes [1], which rises with age, diabetes duration, and impaired quality of metabolic control [2]. The etiological agent of DPN is concerned about serious long-term hyperglycemia and the factors caused by it, which include metabolic disorder, abnormal microcirculation, deficiency of neurotrophic factors, increased free radical oxidative stress, and autoimmune disorder. Apart from diabetes, the predominant risk factors are age, obesity, and peripheral arterial disease [3]. The incidence of DPN increases year by year. Currently, the joint intervention of related drugs is the commonly used treatment, which includes antidepressants, such as tricyclic antidepressants, serotonin norepinephrine inhibitors (SNRIs), and anticonvulsive drugs, such as gabapentin and pregabalin. Opioids can be taken if necessary.

Sustained-release (SR) oxycodone tablet is a pure opioid receptor agonist. It acts on opioid μ receptors and has analgesic effects, and there is no ceiling dose effect. SR oxycodone tablets are widely used in analgesic treatment for patients with cancer as well as for moderate to severe refractory noncancer pain. The results of clinical observations generally consider SR oxycodone tablets effective and safe in the treatment of refractory pain [4–6]. In China, due to a lack of clear understanding about the use of opioids and concerns about iatrogenic addiction and drug abuse, the treatment of the pain caused by DPN with SR oxycodone tablets is not a standard remedy [7]. Therefore, it was necessary to carry out postmarketing clinical observations on SR oxycodone tablets.

This is a multicenter, open-labeled study to observe the clinical use of SR oxycodone tablets for DPN and to assess the efficacy and safety of oxycodone tablets. The objective is to guide clinical application.

Materials and Methods

Case Selection

Patients with moderate to severe DPN must satisfy the following inclusion criteria: 1) patients with confirmed diagnosis of moderate to severe pain (“average pain over the last 24 hours” score before starting of the study: numeric rating scale (NRS) score ≥ 5) caused by DPN; 2) aged over

40 years, the history of pain is more than 4 weeks; 3) to be able to communicate with physicians and sign the informed consent form.

The exclusion criteria are the following: 1) patients who receive treatment with long-acting opioid analgesic formulations; 2) pregnant or lactating women. 3) having history of opioid drug abuse; 4) having history of opioid drug abuse; 4) patients with a history of the following conditions: hypo-oxygenic respiratory suppression, head injury, paralytic ileus, acute abdominal syndrome, stomach empty delay, chronic obstructive pulmonary disease, cor pulmonale, chronic bronchial asthma, high carbonic acidemia, moderate to severe liver dysfunction, severe renal insufficiency (creatinine clearance rate <10 mL/min, severe constipation; concomitant use of mono-amine oxidase inhibitors (MAOI), within 2 weeks after discontinuation of MAOI; 5) patients who have contraindication mentioned in oxycodone hydrochloride SR tablets (OxyContin[®]) package insert, which in the opinion of the investigator, exposes the patient to risk by participating in the study; 6) allergy to oxycodone hydrochloride or other ingredients in the oxycodone hydrochloride SR tablets; and 7) other conditions that violate the relevant regulations of China.

This study was completed in 12 hospitals in China between October 2009 and December 2010.

Drug Administration

Oxycodone hydrochloride SR tablets (OxyContin[®] tablets; tablets were provided by Mundipharma (China) Pharmaceutical Co. Ltd., Beijing, China). The determination of patient initiation dosage should be conducted by study doctors basing on the individualization principle. For opioid-naïve patients with NRS pain scores between 5–6, the initial recommended dose of SR oxycodone tablets is 5 mg/12 hours. For opioid-naïve patients with NRS pain scores between 7–10, the initial recommended dose of SR oxycodone tablets is 10 mg/12 hours. If the patients had been on other opioid analgesics and showed a poor tolerability, patients could be switched to SR oxycodone tablets according to the dosage-conversion table.

For patients who did not achieve adequate pain relief at the initial dose, upward titration was used until stable pain control was achieved. If the initial dose was 5 mg, the dose could be directly increased to 10 mg; if the initial dose was 10 mg, the amount added was equal to 25–50% of the original dose. If pain could not be relieved obviously after a dose was added, the amount would be increased by 25–50% of the original dose in accordance with the principle of dose increasing. The reset followed by analogy. In cases of needing to control breakthrough pain with a frequency of more than twice a day, the next oxycodone dose was increased. IR opioid (e.g., IR morphine) could be used as rescue analgesic for breakthrough pain, at a dose equal to one quarter to one third of a SR oxycodone hydrochloride tablet in 12 hours.

Oxycodone for Diabetic Peripheral Neuropathy

During the study treatment period, other analgesic should be avoided. If it is really necessary, nonsteroidal anti-inflammatory drugs or/and antidepressant drugs could be prescribed.

According to the World Health Organization three-ladder principal for pain management, some medications should be prescribed to prevent side effects, such as cephalexin hydrochloride 10 mg, tid; senna leaf. To prevent the gastrointestinal side effects, SNRIs could be prescribed as well.

The patients were visited every week. The observational period was 6 weeks.

Data Collection and Outcome Measures

Data recorded include days, dosage, analgesic efficacy, and combination therapy when patients are treated with SR oxycodone tablets.

1. Time to onset, analgesic duration, and time required to reach steady-state dose of SR oxycodone tablets for moderate to severe DPN were observed.
2. Pain intensity evaluation: 0–10 NRS was used. 0 means no pain and 10 means most severe pain. Subjects were required to record pain intensity in detail every 24 hours. Patients were followed up once a day during the first week, two to three times in the second week and then once a week. The follow-up continued for 6 weeks.
3. Sleep quality evaluation: The Pittsburgh Sleep Quality Index (PSQI) was used [8], which has been validated as differentiating from “poor” (PSQI > 5) to “good” (PSQI ≤ 5) sleep.
4. Safety evaluation: all the adverse events, including seriousness and causality, were recorded. Respiration, blood pressure and heart rate were recorded if necessary.

Efficacy Evaluation

Primary efficacy endpoint: change in pain intensity every week during the 6-week treatment.

Secondary efficacy endpoints:

1. Time to onset, analgesic duration, and time required to reach steady-state dose of SR oxycodone tablets after the first medication dose.
2. Changes in sleep quality during treatment.
3. Changes of dosage during treatment.

Statistical Analysis

Statistical analysis was performed by SAS V 8.2 (SAS Institute Inc., Cary, NC, USA) for Windows statistical software package and the data expressed as mean ± standard error.

1. Descriptive statistics was performed for the weed-out or dropout cases one by one.

2. Comparability: the value on day 0 was recorded as the baseline value. Every follow-up data was compared with it. According to statistics requirement, χ^2 test, exact probability or nonparametric statistical analysis was performed to analyze the comparability and test standard was 0.05.
3. Safety: descriptive statistics was performed for adverse events and severe adverse events.

Results

Demographics and Baseline Characteristics

Eighty patients satisfying the inclusion criteria were enrolled by 12 hospitals, which participated in the study. Twenty-six patients did not complete the 6-week follow-up, in which seven patients terminated the study prematurely due to pain relief, 17 patients were lost to follow-up

Table 1 Demographics and baseline characteristics of 80 patients with diabetic peripheral neuropathy

Item	Classification	N	Percentage or ($\bar{x} \pm s$)
Gender	Male	40	50
	Female	40	50
Age	(Year)	80	61.8 ± 10
Weight	(kg)	72	62.28 ± 8.75
Hospitalization	Inpatient	47	58.75
	Outpatient to inpatient	1	1.25
	Outpatient	21	26.25
	Inpatient to outpatient	11	13.75
Time of diabetes diagnosis	Months	80	98.38 ± 69.14
Duration of DPN	Within 4 weeks	.	.
	4–6 weeks	19	23.75
	7–12 weeks	3	3.75
	3–6 months	6	7.5
	Over 6 months	52	65
Nature of pain	Numb pain	19	23.75
	Burning pain	11	13.75
	Prickling pain	9	11.25
	Knifelike pain	12	15
	Mixed pain	26	32.5
	Others	3	3.75
Location of pain	Feet	39	48.75
	Upper limbs	13	16.25
	Lower limbs	51	63.75
	Others	3	3.75
Had used analgesics?	Yes	28	35
	No	52	65
Had used other drugs?	Yes	42	52.5
	No	38	47.5

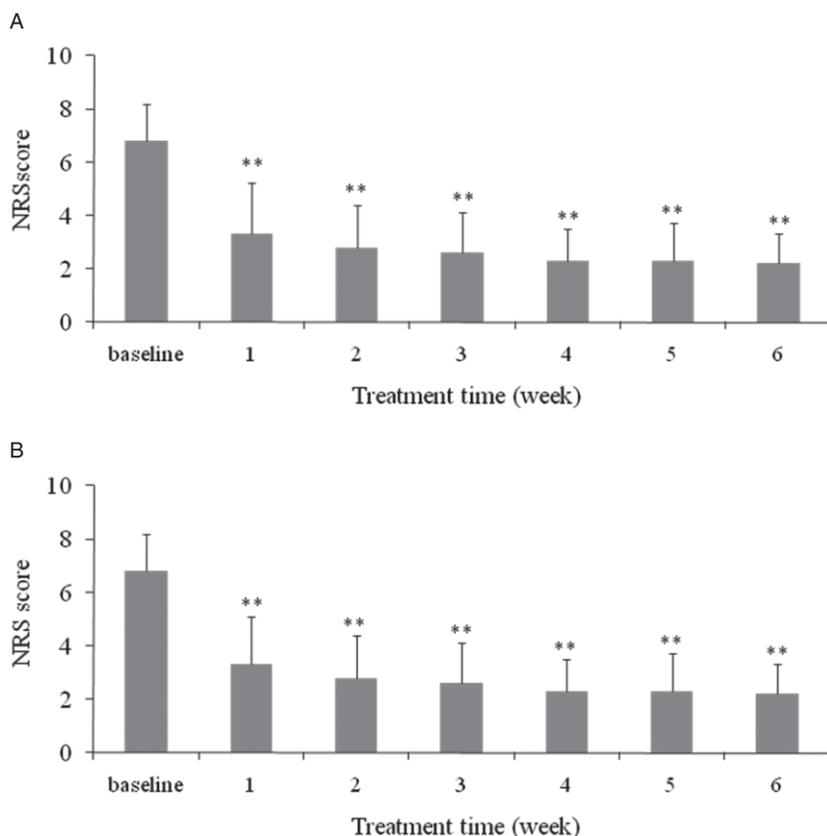


Figure 1 (A) Changes of pain intensity during 6-week SR oxycodone tablets treatment of diabetic peripheral neuropathy (ITT). (B) Changes of pain intensity during 6-week SR oxycodone tablets treatment of diabetic peripheral neuropathy (PP). *Rank-sum test is used to compare the changes of pain score between each week and baseline.

after discharge, one patient had lack of efficacy, and one patient refused to continue his medication because of adverse reactions.

Patients' gender, age, weight, clinical diagnosis, nature of pain, and analgesics use before treatment are shown in Table 1.

Analgesic Effect

Pain Intensity

Before treatment, the average baseline score of pain intensity was 6.8 ± 1.4 , which was moderate to severe pain. After medication for 1 week, pain was significantly relieved in ITT and PP sets, and pain intensity was decreased below 3, to 2.8 ± 1.6 , and lasted to the end of treatment. Statistical analysis showed that the difference between pre- and posttreatment was significant (Figure 1A,B).

Drug Efficacy

After taking SR oxycodone tablets, time to onset was within 45 minutes in nearly 60% of patients, and within 1 hour in nearly 95%. More than 90% of patients achieved stable analgesic dose within 3 days. After reaching the stable dose, the duration of pain relief lasted 12 hours in

more than 90% of patients after every medication dose (Figures 2A,B, 3A,B, and 4A,B).

Sleep Quality

Due to pain, sleep is disturbed to varying degrees in more than 90% of patients before medication. After using oxycodone tablets for 1 week, sleep quality was significantly improved (Figure 5A,B).

Dose Modification

In this study, small doses were required to be used at initial stage. Dose modification was done according to degree of pain relief and adverse reactions. Figure 6 shows that 38 patients increased medication doses in week 1, and 20 patients increased in week 2, while six reduced doses in week 2. In week 3, fewer patients increased doses for stable analgesic effect. Only one patient reduced dose for adverse reaction. Due to pain relief, a small number of patients reduced doses mid course.

Figures 7 and 8 showed that in week 1, the average dose of SR oxycodone tablets of 80 patients was 16.63 ± 7.79 mg. The average daily dose of most patients was about 20 mg after 2 weeks, and that of 3–5 patients was above 30 mg.

Oxycodone for Diabetic Peripheral Neuropathy

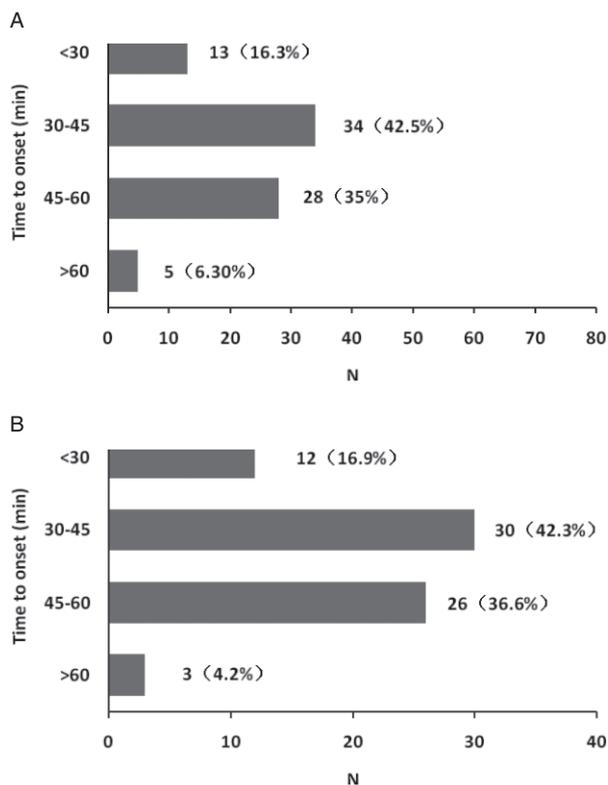


Figure 2 (A) The first onset time of SR oxycodone tablets in treatment of diabetic peripheral neuropathy (ITT). (B) The first onset time of SR oxycodone tablets in treatment of diabetic peripheral neuropathy (PP).

Safety Analysis

In all the enrolled patients, 38 had adverse reactions, and the incidence rate was 47.5%. The main adverse reactions were nausea, vomiting, and constipation, followed by dizziness, dry mouth, urine retention, febrile reaction, etc. There were no serious adverse reactions (Figure 9).

Discussion

SR oxycodone tablet, a potent opioid analgesic, has dual action of sustained release, which is different from general SR medicine. 38% of the drug is released faster and absorbed rapidly with rapid onset, which usually provides analgesia within 1 hour. 62% of the drugs, as slower prolonged release, have long duration of action, and the analgesic effect can be sustained for 12 hours. The steady-state serum concentration is achieved in a short time, with little fluctuation between peak and valley values. Drug absorption is not influenced by food and pH of gastrointestinal fluid, and bioavailability is about 50% which is two times that of morphine. The elimination half-life of oxycodone hydrochloride SR tablets is short, an average of 4.5 hours. There is a positive correlation between dosage and peak serum concentration and the

area under the concentration time curve. Oxycodone hydrochloride SR tablets are taken every 12 hours, and the fluctuation between peak and valley values is comparable to that of immediate release oxycodone administered every 6 hours, so it is easy to predict, perform dose titration, and maintain therapy. The metabolites with little activity have no clinical pharmacological effects on organism and no known damage on vital organs such as liver and kidney. So oxycodone hydrochloride SR tablets can be used for long-term treatment of chronic intractable pains such as DPN without accumulation of metabolites.

Eighty patients with moderate to severe DPN were enrolled in this multicenter, open-labeled study. Twenty-six patients did not complete the 6-week observation period. Among these patients, one discontinued therapy for lack of efficacy, one withdrawn from the trial for adverse reaction, and the rest did not need to continue drug treatment for pain relief (discharge) or switched to non-opioid therapy. During the study, diabetic patients were permitted to be treated for related diseases, such as using insulin and other drugs to control blood glucose or using laxative and control nausea and vomiting drugs to prevent adverse reactions.

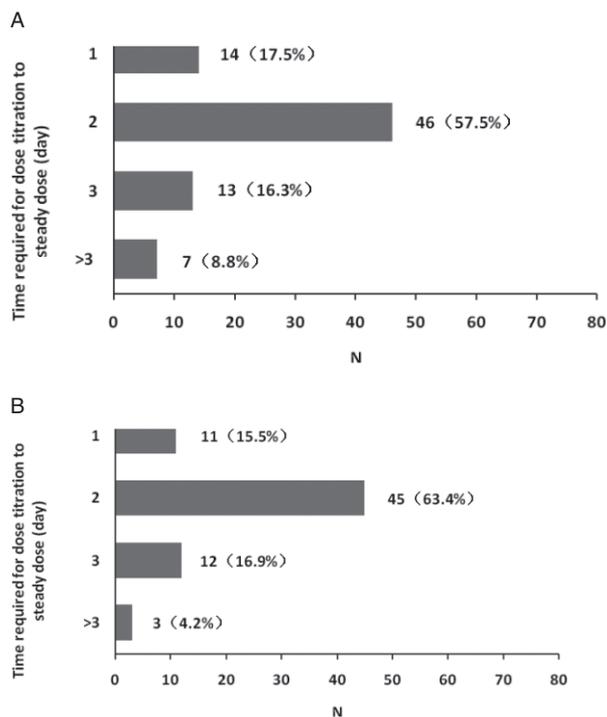


Figure 3 (A) The time required by SR oxycodone tablets in treatment of diabetic peripheral neuropathy for dose titration up to steady dose (ITT). (B) The time required by SR oxycodone tablets in treatment of diabetic peripheral neuropathy for dose titration up to steady dose (PP).

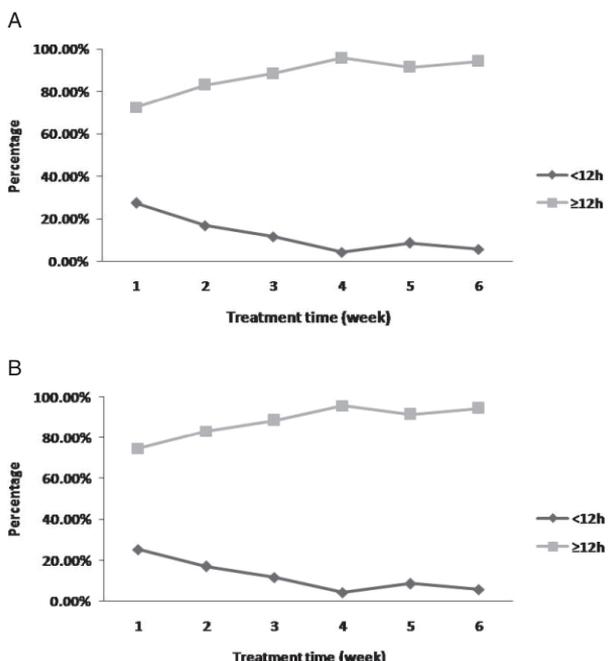


Figure 4 (A) The duration of pain relief for SR oxycodone tablets in treatment of diabetic peripheral neuropathy after each medication (ITT). (B) The duration of pain relief for SR oxycodone tablets in treatment of diabetic peripheral neuropathy after each medication (PP). The exact probability analysis is used to compare the duration of pain relief between each week and week 1 after medication. Remission time is divided into <12 hours and ≥12 hours.

As for dosage and administration, the principle in this analgesic drug trial is the same as that of other potent analgesics, and dose titration method is used. The initial doses are 5–10 mg, and drugs taken orally every 12 hours. Dose modification is done according to clinical situation of adverse reactions and condition of pain relief. Dose escalation will be allowed with 5–10 mg when NRS score of pain intensity is more than 3, and dose reduction will be done when adverse reactions are too hard to tolerate. Oxycodone hydrochloride SR tablets have a fast onset, and the effect is stable and long lasting. After less than 1 week of continuous use, the therapy can reach steady state. The observation results of 80 patients showed that generally, patients taking about 20 mg SR oxycodone tablets daily can effectively control the DPN, and a small number of patients need 30–40 mg daily, which are consistent with the available literature [9,10].

With regard to drug adverse reactions, 38 patients had adverse reactions in this study, and the incidence rate was 47.5%. Two patients had dosage reduced for adverse reactions. Due to the combined use of other drugs such as oxycodone and acetaminophen tablets, tramadol, amitrip-

tyline, bucinazine, gabapentin, and other drugs, the relationship of some adverse reactions to oxycodone hydrochloride controlled-release tablets is only possible. The clinical manifestations of adverse reactions included nausea (18.75%), vomiting (5.00%), constipation (25%), dizziness (10%), dry mouth (1.25%), urine retention (1.25%), febrile reaction (1.25%), etc. One case of nausea and vomiting and one case of febrile reaction were persistent in the whole treatment duration, two cases of constipation lasted continuously in the study duration, and other adverse reactions were relieved within 1–2 weeks. There were no serious adverse reactions such as respiratory depression, which are consistent with the reports of foreign literature [9,11]. All these indicate that oxycodone SR tablets are safe for the treatment of moderate to severe DPN. Prophylactic therapy can be used for nausea, vomiting, constipation, and other adverse reactions.

On addiction and tolerance in this study, some patients switched to opioid analgesics with low μ receptor affinity such as tramadol, bucinazine, and others after stopping

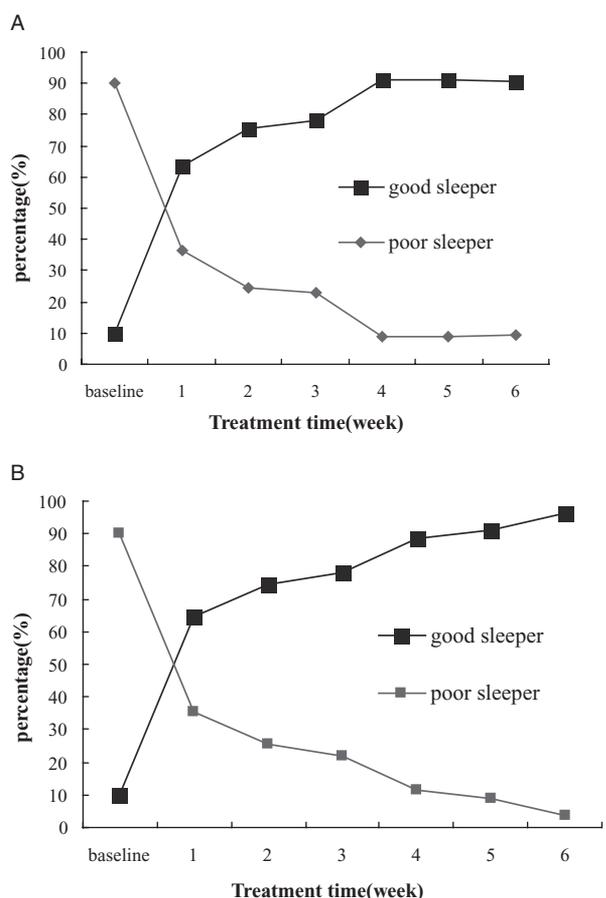


Figure 5 (A) Sleep quality of patients with diabetic peripheral neuropathy treated by oxycodone tablets (ITT). (B) Sleep quality of patients with diabetic peripheral neuropathy treated by SR oxycodone tablets (PP).

Oxycodone for Diabetic Peripheral Neuropathy

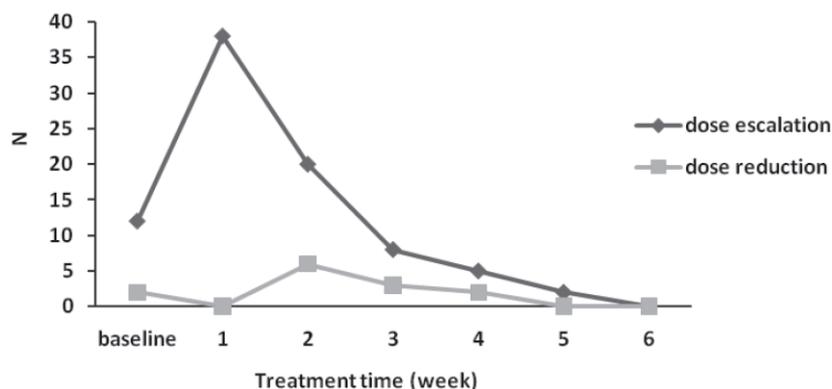


Figure 6 An analysis on the causes of dose modification of SR oxycodone tablets during the 6-week treatment of diabetic peripheral neuropathy (ITT). Cause analysis of dose modification at different week is compared with baseline. The data of “dose reduction due to adverse events” and “gradual dose reduction” are too less to analyze, so the two data are integrated and compared with “dose escalation” for the exact probability.

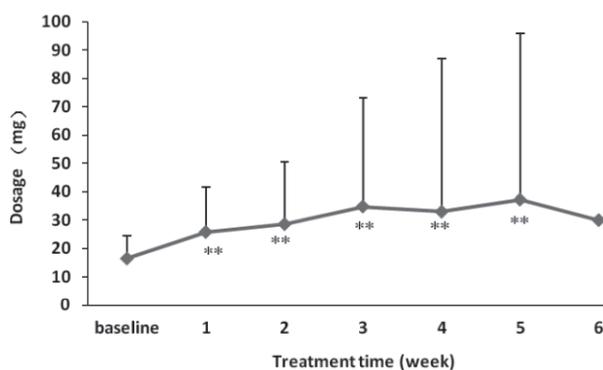


Figure 7 Dose modification of SR oxycodone tablets during the 6-week treatment of diabetic peripheral neuropathy (ITT). Rank-sum test is used to compare the difference between each week and baseline.

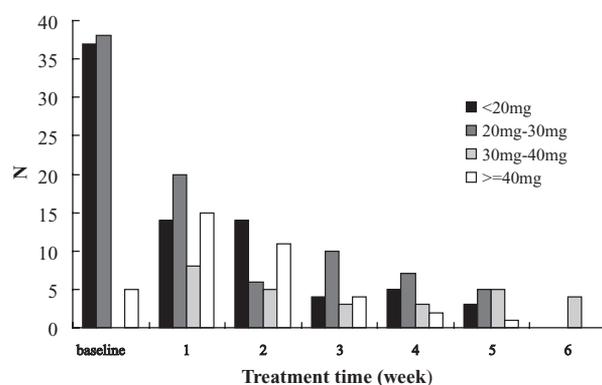


Figure 8 The distribution of SR oxycodone tablets dose adjustment during 6-week treatment of diabetic peripheral neuropathy (ITT).

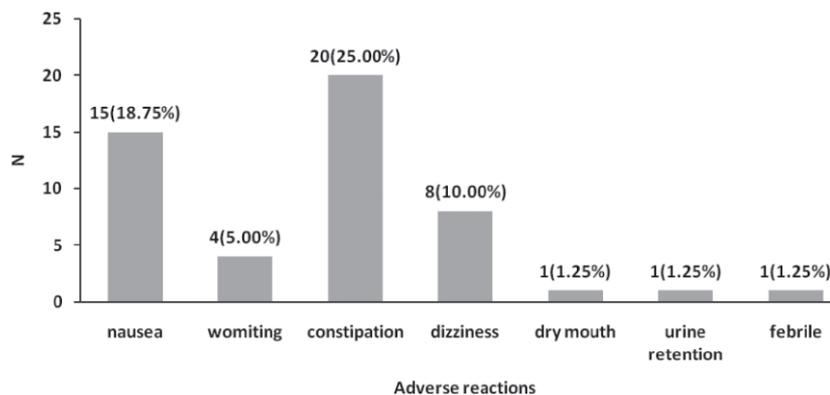


Figure 9 Adverse reactions occurred in patients.

using SR oxycodone tablets. Since the drug transition from opioid with high μ receptor affinity to opioid with low μ receptor affinity, although potent opioid oxycodone was used for 6 weeks, there was no drug withdrawal syndrome nor drug craving or drug-seeking behavior. SR oxycodone tablets used for chronic noncancer pain, if it is done correctly, the problem of iatrogenic addiction can be avoided. The dosage in this study was decreased gradually, and there was no drug resistance phenomenon.

In the past in China, potent opioid analgesics can only be used for chronic cancer pain and various acute noncancer pains and potent opioid analgesics cannot be used for chronic noncancer pain for long term. Now in China, SR oxycodone tablets have been approved for the treatment of moderate to severe chronic pain [12] and the period of continuous use cannot exceed 8 weeks [13]. Appropriate use of SR oxycodone tablets provides an opportunity for patients with moderate to severe chronic noncancer pains to legitimately use potent opioid analgesics. The results of this clinical observation further elaborated the efficacy and safety of SR oxycodone tablets in the treatment of moderate to severe DPN. When using this class of drug, doctors should abide by "the guiding principle of strong opioids in treatment of chronic noncancer pain" promulgated by the State Food and Drug Administration to strictly select indications and strictly comply with the precautions, so they can safely and effectively use potent opioid analgesics for noncancer pain patients.

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